UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/678,756	10/02/2003	Mary Jo Ondrechen	NU-593XX	6620

207 7590 03/22/2007
WEINGARTEN, SCHURGIN, GAGNEBIN & LEBOVICI LLP
TEN POST OFFICE SQUARE
BOSTON, MA 02109

EXAMINER	
AGRAWAL, RITESH	
ART UNIT	**PAPER NUMBER**
1631	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

## *Office Action Summary*	**Application No.** 10/678,756	**Applicant(s)** ONDRECHEN ET AL.	
	Examiner Ritesh Agrawal	**Art Unit** 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 04 January 2007.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-16 is/are pending in the application.
   4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) 1-16 is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.
10)☒ The drawing(s) filed on 1/4/07 is/are: a)☒ accepted or b)☐ objected to by the Examiner.
   Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
   Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a)☐ All b)☐ Some * c)☐ None of:
      1.☐ Certified copies of the priority documents have been received.
      2.☐ Certified copies of the priority documents have been received in Application No. _____.
      3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
   * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
   Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
   Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' amendment and request for reconsideration in the communication filed on 1/04/07 are acknowledged and the amendments entered.

Claims 1-16 are currently pending and under consideration.

Declaration under 37 C.F.R. 1.132

2. The declaration of Mary Jo Ondrechen, filed 01/04/07, could not be considered because said declaration was not signed.

Withdrawn Rejections

3. The rejection of claims 7-10 under 35 U.S.C. 112, 2nd paragraph, an indefiniteness rejection, is hereby withdrawn in light of the amendments to the claims filed 1/04/07

The rejection of claim 1 under 35 U.S.C. 102 (b) over Oda et al. is withdrawn in light of applicant's arguments (remarks, page 11).

Priority

4. The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the

requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/415,742, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. While said provisional application discloses claims 1-4, 6, 11, and 13-16, it does not disclose claims 5, and 7-10. With respect to claim 12, while said provisional application discloses identification of perturbed titration curves through visual inspection, it does not disclose identification of perturbed titration curved via statistical analysis or automated classification. Prior art published after the claimed prior application but before the filing date of the instant application may have been cited in this Office action. Applicants are requested to provide evidence that the elected invention is indeed disclosed in the prior application if they wish to contest the citation of prior art.

The issue of priority is maintained from the previous Office Action. Applicants have not addressed this issue in their response, filed 01/04/07.

Specification

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicants are required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Such code can be found on page 16 of the specifications and elsewhere.

This objection is reiterated from the previous Office Action. While applicants' amendment addresses some examples of browser-executable code including the one on page 16, it does not address all such instances found in the disclosure. For example see page 7 and 47 of the specification. Applicants are alerted to the fact that these instances simply exemplify the presence of browser-executable code. Applicants are requested to thoroughly check the disclosure for all instances of browser-executable code and delete them.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-16 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. This rejection is newly applied.

The following analysis of facts of this particular patent application follows the analysis suggested in the "Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility"[1]. Note that the text of the Guidelines is italicized.

To satisfy section 101 requirements, the claim must be for a practical application of the § 101 judicial exception, which can be identified in various ways (Guidelines, p. 19):

- The claimed invention "transforms" an article or physical object to a different state or thing.

- The claimed invention otherwise produces a useful, concrete and tangible result, based on the factors discussed below.

In the instant case, the claimed invention does not "transform" an article or physical object to a different state or thing because it merely carries out numerical calculations to determine a property of a protein. This does not preclude the subject matter to be patentable as, for eligibility analysis, as

> *physical transformation "is not an invariable requirement, but merely one example of how a mathematical algorithm [or law of nature] may bring about a useful application." AT&T, 172 F.3d at 1358-59, 50 USPQ2d at 1452. If the examiner determines that the claim does not entail the transformation of an article, then the examiner shall review the claim to determine if the claim provides a practical application that produces a useful, tangible and concrete result. In determining whether the claim is for a "practical application," the focus is not on whether the steps taken to achieve a particular result are useful, tangible and concrete, but rather that the final result achieved by the claimed invention is "useful, tangible and concrete." The claim must be examined to see if it includes anything more than a § 101 judicial exception. If the claim is directed to a practical application of the § 101 judicial exception producing a result tied to the physical world that does not preempt the judicial exception, then the claim meets the statutory requirement of 35 U.S.C. § 101. If the examiner does not find such a practical application, the examiner has determined that the claim is nonstatutory. (Guidelines, p. 20)*

The question is thus whether the final result achieved by the claimed invention satisfies all three criteria of being useful, and concrete, and tangible.

Furthermore, the useful, tangible, and concrete result must be recited in the claim itself, rather than addressed in specification.

(2) **"TANGIBLE RESULT"** The tangible requirement does not necessarily mean that a claim must either be tied to a particular machine or apparatus or must operate to change articles or materials to a different state or thing. However, the tangible requirement does require that the claim must recite more than a § 101 judicial exception, in that the process claim must set forth a practical application of that § 101 judicial exception to produce a real-world result. The opposite meaning of "tangible" is "abstract."

---

[1] Available at http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/guidelines101_20051026.pdf

The instant claims are drawn to computational means for determining putative interaction sites in a protein. However, as claimed, the method does not produce a tangible result. For example, the method as claimed may take place entirely within the confines of a computer or a human mind without any communication to the outside world and without using or making available for use, the results of the computation. Thus, the instant methods of the claims do not produce any tangible result.

Therefore, the final result achieved by the claimed invention does not satisfy all three criteria of being useful, and concrete, and tangible.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-3 and 5-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is newly applied.

The claims are drawn to a method for determining a putative interaction site in a protein requiring the ability to obtain a structure of the protein.

In analysis of claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, regarding genus/species situations, the written description guidelines note that "satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description, which can be obtained from the US PTO website: <http://www.uspto.gov>). Given that the genus essentially includes obtaining the interaction site which requires a structure for the protein but not requiring the structure be known *a priori*, one of ordinary skill in the art would have reasonable doubt applicant had possession of the claimed genus at the time the application was filed. Despite applicant's assertion that proteins examined using the claimed invention "does not have to bear any resemblance in sequence or structure to any previously characterized protein" (specification, page 6, lines 14-16), a truly novel protein with no relatedness to a known protein or structure would require *ab initio* structure prediction to determine its structure. Xu et al. (Current Protein and Peptide Science, Vol. 1, Pages 1-21, 2000) discloses that such prediction mechanisms are extremely difficult and are generally unreliable (for example, see page 15, 2nd column, 1st paragraph, lines 2-6). Furthermore, even if an overall structure could be obtained through homology modeling, Xu discloses that it would be difficult to obtain the structure of the interaction site if the interaction site residues were to lie in a region in which there was an extended gap relative to the protein sequence of the template structure (for example, see page 12, 2nd column, 2nd paragraph, lines 10-12). Given the limitations of the protein arts, applicant's admission that poor quality structures can lead to problems in predicting interaction residues (for example, page 17, lines 11-16), and the fact that applicant hasn't provided any examples of a truly novel protein with unknown structure for which the algorithm makes correct predictions, one of ordinary skill in the art would have considerable doubt that applicant had possession of the claimed genus at the time the application was filed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 1-4, 6, 11, 12, 13-16 are rejected under 35 U.S.C. 102(a) as being anticipated by Ondrechen et al. (2001), (PNAS, 98, 12473-78). This rejection is reiterated and maintained from the prior Office Action. As applicant's arguments against the rejection are based upon the 132 declaration, since the 132 declaration could not be considered (for the reasons addressed above), applicant's arguments are moot with respect to the rejection.

The claims are drawn to a method for determining interaction sites in a protein.

With respect to independent claim 1, Ondrechen et al. disclose, "Analysis of the theoretical microscopic titration curves for all the ionizable residues of these proteins shows that a small fraction (3-7%) of the curves possess a flat region" (Abstract, lines 7-10). This coincides with the limitations of claim 1 to, "[identify] ionizable amino acid residues having anomalous predicted theoretical microscopic titration curve behavior." The reference further discloses, "the THEMATICS method identifies the location of the known active site from the cluster of positive results in coordinate space" (page 12476, 2nd column, 4th paragraph, lines 8-10). This coincides with the additional limitation of claim 1, "clustering certain of said identified ionizable amino acid residues into putative interaction sites."

With respect to dependent claim 2, the method disclosed by Ondrechen et al. comprises, "a computational method that identifies the active site of a protein . . . from a three-dimensional structure" (page 12476, 2nd column, 5th paragraph, lines 1-3); "calculating the pH dependent electrical potential caused by ionizable residues" (page 12477, 1st column, 6th paragraph, lines 1-2) which signifies that in calculating the pH dependent titration curves, an electrical potential function is being calculated. Ondrechen et al. further disclose that, "for each residue type, we have a plot with a family of curves: one plot with a curve for each Lys residue, another plot with a curve for each Arg residue, etc. We compare the curves for residues of the same type; curves with unusual shape are noted by visual inspection," (page 12473, 2nd column, 4th paragraph, lines 10-14). Step f of claim 2 is disclosed as above from page 12476, 4th paragraph, lines 8-10.

The limitations of claim 3 can be inferred from the fact that all residues of all residue types are examined for perturbed titration curve behavior (as cited above) but that only certain residues from this set fall into clusters. Hence, if the citation is identifying all perturbed residues and a subset of these cluster the citation is also identifying perturbed titration curve residues that do not cluster. As an example from the reference, for the TIM protein, four residues His-95, Glu-165, Lys-112 and Tyr-164 have perturbed curves (page 12474, 1st column, 4th paragraph, lines 2-4) but only three of the four cluster spatially, "Three of the four residues with perturbed titration curves are in close spatial proximity," (page 12474, 2nd column, 2nd paragraph, lines 1-2).

The limitations of claim 4 are disclosed in the abstract, "We show that theoretical microscopic titration curves (THEMATICS) can be used to identify active-site residues in proteins of known structure."

The limitations of claim 6 are disclosed in the legend of table 1, "Positive results that form a cluster in coordinate space," (page 12476, table 1, legend).

The limitations of claim 11 are disclosed as, "the perturbed titration curves in which partial protonation persists over a wide pH range," (page 12477, 2nd column, 1st paragraph, lines 27-28).

A species of claim 12 is disclosed as above on page 12473, 2nd column, 4th paragraph, lines 10-14.

The limitation of claim 13 is inferred from the reference to a catalytic site, "but is far enough away from the catalytic site, " (page 12476, 1st column, 1st paragraph, lines 2-3) in the discussion of identified active site residues.

The limitation of claims 14-15 is disclosed as, "K258 of 1AMQ is the residue that binds the cofactor," (page 12476, table 1, legend) wherein recognition must occur for binding to the cofactor.

In the absence of an explicit definition of the term ligand one where the term refers to anything that binds to a protein will be used. As such, the disclosure as stated above for claim 15 applies as a disclosure for claim 16 as well.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ondrechen et al. (2001), (PNAS, 98, 12473-78) as applied to claims 1-4, 6, 11, 12, 13-16 above, and further in view of Sali (1998), (Nature Structural Biology, 5, 1029-1032). This rejection is reiterated and maintained from the prior Office Action. As applicant's arguments against the rejection are based upon the 132 declaration, and since the 132 declaration could not be considered (for the reasons addressed above), applicant's arguments are moot with respect to the rejection.

Claim 5 is drawn to a method for identifying protein active site residues from a protein structure where the protein structure is predicted from the amino acid sequence.

Ondrechen et al. disclose a method for identifying protein active site residues from a protein structure but do not disclose the prediction of said structure from a protein's amino acid sequence.

Sali teaches that," useful model [structures] can be obtained by fold assignment and comparative modeling for those protein sequences that are related to at least one known protein structure," (page 1029, 1st column, 1st paragraph, lines 10-14).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the predictive method of Ondrechen et al. such that they allowed for the determination of a protein's structure from its amino acid sequence. One having ordinary skill in the art would have been motivated to do this because, as suggested by Sali, " it is not feasible to determine the structure of every protein by experiment," and obtaining structures from amino acid sequence would allow one to analyze, "three-dimensional models for hundreds of thousands of . . . proteins, " from 10,000 protein structures, (page 1029, 1st column, 1st paragraph, lines 15-18).

Conclusion

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ritesh Agrawal whose telephone number is (571) 272-2906. The examiner can normally be reached on 8:30 AM - 5:00 PM M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ritesh Agrawal, PhD RA

SHUBO (JOE) ZHOU, PH.D.
PATENT EXAMINER